

BEST AVAILABLE COPY**Remarks/Arguments**

Claims 52-58, 60-68, 70-78, 80-93 and 96 are pending in the Application.

Claims 52-55, 60-66, 70-75, 80-93, 95 and 96 stand rejected.

Claims 56-58, 67, 68 and 76-78 are objected to.

Claims 52, 54-55, 62, 64-65, 67, 72, 74-75, 77, 86, and 88-89 are amended herein.

Claims 53, 63, 73, and 87 are cancelled herein.

I. REJECTIONS UNDER 35 U.S.C. §§ 102(a) AND 103(a) OVER CHEN

In the Office Action, the Examiner has rejected Claims 52-55, 60-66, 70-75, 80-93, 95 and 96 under 35 U.S.C. § 102(a) as being anticipated by or, in the alternative under 35 U.S.C. § 103(a) as being obvious over Chen *et al.*, “Chemical attachment of organic functional groups to single walled carbon nanotube material,” *Journal of Materials Research*, Vol. 13, No. 9, Sept. 1998, pp. 2423-2431 (“Chen”). Office Action, at 2.

Anticipation under 35 U.S.C. § 102(a) requires each and every element of the claim to be found within the cited prior art reference.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), at least three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *see also* M.P.E.P. §§ 2143-2143.03.

The Examiner contends that “Chen teaches on the next-to-last page a Birch reduction experiment which appears to possess the claimed functional loading, given the elemental analysis. (The other experiments appear to have one group per 35-50 carbons, so do not meet the claims.)” *Id.*

Regarding *Chen*, Applicant again repeats its response expressed in pages 2-4 of its 1.111 Amendment filed August 20, 2004 (“the August 4, 2004 Amendment”). In the August 4, 2004

Amendment, the Applicant presented various citations in *Chen* to illustrate that, although *Chen* had hoped to functionalize the SWNT, *Chen* repeatedly admitted no certainty in actually accomplishing that result. August 4, 2004 Amendment, at 2-4. Applicant pointed out specifically why *Chen* was not in possession of sidewall functionalized single wall carbon nanotubes. *Id.*

Notwithstanding the above-mentioned arguments, the elemental analysis cited by the Examiner found on the next-to-last page of *Chen* is found in the last sentence of the paragraph headed by: “3. Birch reduction (2).” With all due respect, the elemental analysis that the Examiner is referring to appears erroneous. One of ordinary skill in the art would recognize that this elemental analysis is erroneous and nonsensical. One of the errors involves the element fluorine, which is not part of the single-wall carbon nanotube material, the added chemical reactants or solvents, or the reactor vessel. The second problem with the elemental analysis is that it does not relate to what is bonded to the single-wall carbon nanotubes. In fact, the elemental analysis is nonsensical if the moieties were assumed to be bonded to the single-wall carbon nanotubes, because the amount of bonding would be greater than the theoretical limit of one substituent per two carbons and result in the destruction of the single-wall carbon nanotubes. One of ordinary skill in the art would recognize that this elemental analysis is flawed and requires interpretation based on the actual “reduction” chemistry done on the single-wall carbon nanotube material.

The Applicant, therefore, contends that some of the data in this elemental analysis appear completely incorrect and other components of the data cannot and do not relate to moieties or substituents covalently bonded to the single-wall carbon nanotube material. More detail regarding these two contentions is given below.

- (1) First, regarding fluorine in the elemental analysis, the elemental states 8.32% F. As there is no source of fluorine in the method or components recited, this appears to be an error in the stated elemental analysis. That the nitrogen in the elemental analysis is also stated to have the same content of 8.32%, and, that it would be highly unlikely that two elements would have exactly the same component percentage in a sample, the inclusion of fluorine in the elemental analysis appears to be an error in proofing

the *Chen* article.

- (2) Second, although the elemental analysis of *Chen* includes an amount of N (nitrogen), the chemical method is a **reduction**, which adds **hydrogen** to double bonds, **not nitrogen**. Although *Chen* cites the reduction method to be a “Birch reduction (2),” the method is actually more specifically known as the “Benkeser” reduction. Both the Birch and the Benkeser reductions are known reduction methods, and both attack double bonds and form carbon-hydrogen bonds. In the Birch reduction, the solvent is liquid ammonia, and, in the Benkeser reduction, the solvent is a primary amine, of which ethylamine and ethylenediamine are the most commonly used. These solvents are used because the lithium used in these reductions dissociates “more or less completely into Li^+ and solvated electrons.” (See “Handbook of Reagents for Organic Synthesis Oxidizing and Reducing Agents” Edited by S. D. Burke and R. L. Danheiser, John Wiley & Sons, New York, 1999, p. 195, col. 2 and p. 196, col. 1, attached as **Exhibit A**.)
- (3) Because ethylenediamine is a **solvent** in the reduction cited in *Chen*, neither ethylenediamine nor fragments of ethylenediamine is bonded to the single-wall carbon nanotubes and, therefore, consequently, nitrogen is not bonded to the single-wall carbon nanotubes. One of ordinary skill in the art would recognize that the cited “Birch” reduction (actually a Benkeser reduction) would attack double bonds and form carbon-hydrogen bonds, not bonds with carbon or nitrogen. Therefore, one of ordinary skill in the art would recognize that this reduction method would not form a covalent bond with the carbon or nitrogen atoms in the ethylenediamine molecule.
- (4) Since the ethylenediamine in the *Chen* “Birch reduction (2)” (actually a Benkeser reduction), remains intact as a solvent, nitrogen does not bond to the carbon nanotube material. However, ethylenediamine has a propensity to stick or adhere non-covalently to carbon nanotubes, even after copious rinsing. Although not bonded to the carbon nanotube material, ethylenediamine adsorbs and adheres quite tenaciously

to the carbon nanotubes, and, thus, it is not surprising that it would still be present in the washed single-wall carbon nanotube material as ethylenediamine, and be part of the elemental analysis of the sample. This propensity to adhere to the nanotubes can explain the nitrogen in the elemental analysis.

- (5) If one attributes all the nitrogen to adsorbed ethylenediamine and backs out the appropriate number of moles of carbon and hydrogen to correspond to the stoichiometry of ethylenediamine ($C_2N_2H_8$), then the remaining hydrogen in the sample analysis is plausible for the reduction reaction, *i.e.*, one hydrogen atom to about 10 carbon atoms.
- (6) If the ethylenediamine is not backed out of the elemental analysis and the full amount of hydrogen (H) were bonded to the nanotubes, the ratio would be one hydrogen atom to 1.42 carbon atoms. The theoretical limit for full substitution on a single-wall carbon nanotube is one substituent per 2 carbons. Higher substituent level causes the bonds in the nanotube wall to break and, thereby to destroy the integrity of the single-wall carbon nanotubes. Without backing out the adsorbed ethylenediamine, this higher level of substitution (*i.e.*, 1 H to 1.42 C) would be nonsensical because the single-wall carbon nanotubes would be destroyed.

Therefore, in summary, one of ordinary skill in the art would recognize that the fluorine reported in the elemental analysis of *Chen* is erroneous and that the nitrogen in the elemental analysis in the “Birch reduction (2)” of *Chen* does not relate to bonded nitrogen, but rather adsorbed ethylenediamine.

However, assuming, for the sake of argument, the scenario wherein hydrogen atoms are covalently bonded to the sidewall of the single-wall carbon nanotubes in *Chen*, Applicant has amended independent Claim 52 to include the elements of Claim 53, which lists substituents, none of which are hydrogen. (Accordingly, Claim 53 is hereby cancelled.) Furthermore, *Chen* does not teach or suggest the claimed substituents in the claimed ratios of Claim 52. Claims 54 and 55 were amended to depend from Claim 52 instead of cancelled Claim 53.

Likewise, Applicant has also amended independent Claim 62 to include the elements of Claim 63, which lists substituents, none of which are hydrogen. (Accordingly, Claim 63 is hereby cancelled.) Furthermore, *Chen* does not teach or suggest the claimed substituents in the claimed ratios of Claim 62. Claims 64 and 65 were amended to depend from Claim 62 instead of cancelled Claim 63.

Likewise, Applicant has also amended independent Claim 72 to include the elements of Claim 73, which lists substituents, none of which are hydrogen. (Accordingly, Claim 73 is hereby cancelled.) Furthermore, *Chen* does not teach or suggest the claimed substituents in the claimed ratios of Claim 72. Claims 74 and 75 were amended to depend from Claim 72 instead of cancelled Claim 73.

Likewise, Applicant has also amended the independent Claim 86 to include the elements of Claim 87, which lists substituents, none of which are hydrogen. (Accordingly, Claim 87 is hereby cancelled.) Furthermore, *Chen* does not teach or suggest the claimed substituents in the claimed ratios of Claim 86. Claims 88 and 89 were amended to depend from Claim 86 instead of cancelled Claim 87.

Regarding amended Claims 52, 62, 72 and 86, *Chen* does not teach or suggest the claimed substituents in the claimed ratios. Thus, Claims 52, 62, 72 and 86, as amended, are neither anticipated nor *prima facie* obvious over *Chen*.

Likewise, Claims 54-55, which are dependent upon amended Claim 52, Claims 64-66, which are dependent upon amended Claim 62, Claims 74-75, which are dependent upon amended Claim 72, and Claims 88-93 and 95-96, which are directly or indirectly dependent upon amended Claim 86, are also neither anticipated nor *prima facie* obvious over *Chen* for the same reasons that independent Claims 52, 62, 72 and 86, as amended, are neither anticipated or *prima facie* obvious over *Chen*.

Regarding Claims 54 and 55, the Examiner notes that "Claims 54 and 55 do not require that the linear chain embodiment be chosen." Office Action at 2. To that end, the Applicant has amended Claims 54 and 55 to require the embodiments cited in Claims 54 and 55 to be chosen.

Therefore, as a result of the foregoing, Applicant respectfully requests that the Examiner withdraw his rejection of Claims 52, 54-55, 60-62, 64-66, 70-72, 74-75, 80-86, 88-93, 95 and 96

under 35 U.S.C. § 102(a) as being anticipated by, or in the alternative under 35 U.S.C. § 103(a) as obvious over *Chen*.

II. SUGGESTED AMENDMENTS

Examiner states that “Claims 67 and 77 are interpreted to require a metal in the product,” and that “[a]mendment to this end is suggested.” Office Action, at 2.

As suggested by the Examiner, Applicant has herein amended Claims 67 and 77 for clarity by including the phrase “such that the product comprises a complexed metal.” Applicant respectfully asserts that the amendments to Claims 67 and 77 are not narrowing amendments made for a reason related to the statutory requirements for a patent that will give rise to prosecution history estoppel. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 122 S. Ct. 1831, 1839-40, 62 U.S.P.Q.2d 1705, 1711-12 (2002).

III. OBJECTED TO CLAIMS

The Examiner has indicated that Claims 56-58, 67, 68 and 76-78 are objected to. Office Action, at 2. The Examiner has apparently objected to these claims in that they are dependent claims that depend (directly or indirectly) from rejected independent claims.

In light of the amendments to independent Claims 52, 62, 72 and 86, from which all of the objected to Claims 56-58, 67, 68 and 76-78 now (directly or indirectly) depend, it is asserted by the Applicant that these dependent Claims 56-58, 67, 68 and 76-78 now depend from allowable independent claims.

In light of the foregoing, Applicant respectfully requests that the Examiner withdraw his objection to Claims 56-58, 67, 68 and 76-78.

IV. CONCLUSION

As a result of the foregoing, it is asserted by Applicant that the Claims in the Application are now in a condition for allowance, and respectfully requests allowance of such Claims.

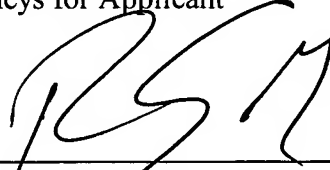
Applicant respectfully requests that the Examiner call Applicant’s attorney at the below listed number if the Examiner believes that such a discussion would be helpful in resolving any remaining problems.

RESPECTFULLY SUBMITTED,

WINSTEAD SECHREST & MINICK P.C.

Attorneys for Applicant

By: _____

A handwritten signature in black ink, appearing to read 'RSG', is written over a horizontal line.

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*Handbook of Reagents
for Organic Synthesis*

*Oxidizing and
Reducing Agents*

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Lithium¹



[7439-93-2]

Li

(MW 6.94)

(powerful reducing agent;¹ used for partial reduction of aromatics and conjugated polyenes;^{1c,m-o} conversion of alkynes to *trans*-alkenes;^{1a,b} stereoselective reduction of hindered ketones;¹¹ enone reduction and regioselective alkylation;^{1f,j} reductive cleavage of polar single bonds^{1a})

Physical Data: mp 180.5°C; bp 1327 ± 10°C; *d* 0.534 g cm⁻³. Natural isotopic composition: ⁷Li (92.6 %); ⁶Li (7.4 %).

Solubility: 10.9 g/100 g NH₃ at -33°C (= 74.1 g/L NH₃); 36.5 g/L MeNH₂ at -23°C.

Form Supplied in: under Ar, as solid in the form of wire, ribbon, rod, foil, shot, ingot, or as a powder; in mineral oil, as wire, shot, or as 25–30 wt % dispersions.

Purification: commercially available in up to 99.97% purity. In general, lithium is not further purified except for cutting off the surface coating.

Handling, Storage, and Precautions: best stored under mineral oil in airtight steel drums and handled under Ar or He. Dispersions in mineral oil segregate on storage and uniformity is restored by stirring. The mineral oil is washed off under Ar with pentane or hexane, and the metal is either dried in an Ar stream or rinsed with the reaction solvent. Dry Li powder is extremely reactive towards air, H₂O vapor, and N₂. The metal reacts rapidly with moist air at 25°C, but with dry air or dry O₂ only at higher temperatures (>100°C). A slight blow can initiate violent burning. Reaction with N₂ already occurs at 25°C, but is inhibited by traces of O₂. Li reacts readily with H₂O, but does not spontaneously ignite as the other alkali metals do. It reacts rapidly

with dil HCl and H₂SO₄ and vigorously with HNO₃. Ready reaction occurs with halogens.

Reducing Systems. For reductions with Li, liquid *Ammonia* or primary amines are most often the solvents of choice. Li dissociates in these solvents more or less completely into Li⁺ and solvated electrons, producing deep-blue metastable solutions.² Etheral solvents (peroxide-free!) such as THF or DME may be used alone, but are usually used as cosolvents with NH₃ or amines. Li solutions in HMPA are quite unstable in contrast to *Sodium* solutions, but are stabilized by THF.³ Reduction occurs by a sequence of single electron and proton transfers to the organic substrate, leading to saturation of multiple bonds or fission of single bonds.^{1a,i,4}

Li-NH₃. Li has a higher normal reduction potential⁵ and molar solubility⁶ in liquid NH₃ than Na or *Potassium* (see Table 1). This permits the use of larger quantities of cosolvents for substrates that are less soluble in NH₃. The concentrations of Li in NH₃ used in reactions vary widely, from 0.1 to 3 g Li/100 mL NH₃. Concentrations near saturation form a second, less dense, bronze-colored phase which is normally avoided.⁷

Table 1 Solutions of Alkali Metals in Liquid Ammonia

Metal	Solubility ⁶ at -33°C (g metal/100 g NH ₃) (g-atom M/mol NH ₃)	Normal reduction potential ⁵ at -50°C (V)
Li	10.9 (0.26)	-2.99
Na	24.5 (0.18)	-2.59
K	47.8 (0.21)	-2.73

Reductions are performed either in the absence or presence (Birch conditions^{1b}) of a proton source, depending on the desired products.^{1a,i,4b} An added proton source can effect reductions which do not occur in its absence (e.g. benzene reduction). It can lead to higher saturation (e.g. in enone reduction) or suppress dimerization and base-catalyzed transformations of primary products. EtOH and *t*-BuOH are the most common proton donors. Primary alcohols protonate the intermediate anions more rapidly, but tertiary alcohols react more slowly with the metal. Other proton donors are NH₄Cl, H₂O, and various amines.^{1a,e,4b}

The order of adding the reagents can influence the product distribution.^{1a} Most often, Li is added last, until the blue color of the solution persists. For less reactive substrates, alcohol addition is delayed (Wilds-Nelson modification).^{5b} The reaction is concluded by quenching excess Li mildly and efficiently with sodium benzoate⁸ or with excess EtOH and then NH₄Cl, and NH₃ is allowed to evaporate.

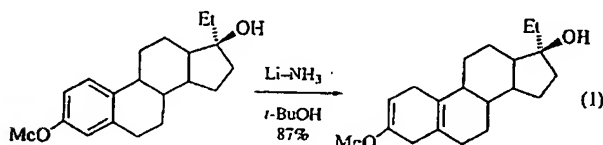
Distillation of NH₃ from Na or through a BaO column removes moisture and iron impurities. The latter catalyze the reaction of alkali metals with the added alcohol and NH₃.² The Li-NH₃-ROH system is less sensitive to traces of iron than Na-NH₃-ROH, which accounts in many instances for its superiority.⁹ *Lithium Amide* is less soluble in NH₃ than *Sodium Amide* and *Potassium Amide*, and base-catalyzed formation of side products is less frequent.^{1g,i} Nevertheless, in many cases similar results are obtained with Li

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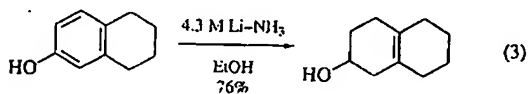
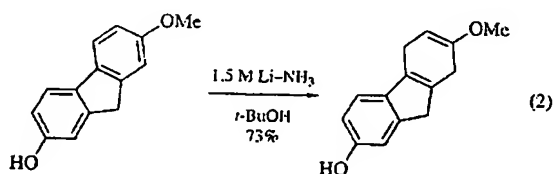
and Na in NH_3 ; Li is preferred for less reactive substrates and Na when overreduction is a problem.¹

Lithium/Primary Amines. Li forms stronger, but less selective, reducing agents with primary amines (Berkner reduction).^{1d,h,k} The higher reactivity is probably caused by higher reaction temperatures^{1i,k} and possibly also by smaller electron solvation.² The reactivity can be modified by addition of alcohols.^{1h} The Li-amine solutions seem more sensitive to catalytic decomposition than Li in NH_3 .¹⁰ The choice of the amine is limited by the solubility of Li; ethylamine and ethylenediamine are most common. Na is hardly soluble in amines (e.g. more than 100 times less soluble in ethylenediamine at room temperature than Li).¹¹ Reactions of calcium in amines have been described.¹²

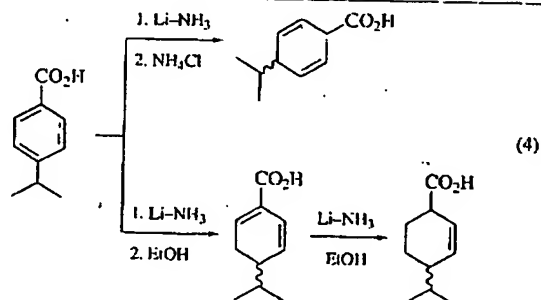
Reduction of Aromatic Compounds^{1,13}. Benzene and its derivatives are reduced to 1,4-cyclohexadienes with Li-NH_3 in the presence of a proton source (see also *Sodium-Ammonia*). Derivatives with electron-donating substituents lead to 1-substituted cyclohexadienes. Thus reduction of anisole derivatives furnishes 1-methoxycyclohexa-1,4-dienes (eq 1).⁹



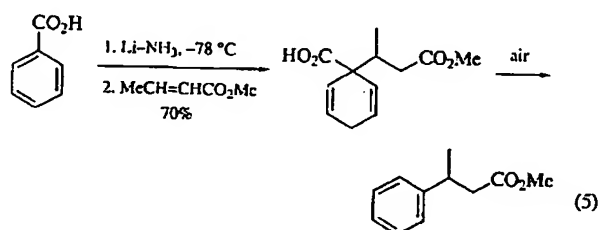
Hydrolysis of such dienol ethers to cyclohex-3-enones or with isomerization to cyclohex-2-enones has found wide application in syntheses of steroids, terpenoids, and alkaloids.^{1f,m} Li is superior to Na for the more difficult reductions of 1,2,3-substituted anisole derivatives,^{5b} though sometimes even excess Li gives poor results.¹⁴ Anisoles are more readily reduced than phenols (eq 2),¹⁵ but higher concentration of Li in NH_3 may effect phenol reduction to cyclohexenols (eq 3).¹⁶



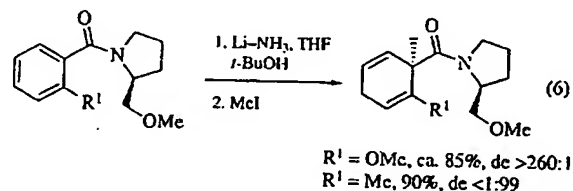
Electron-acceptor substituents enhance reduction rates and promote 1,4-reduction at the substituted carbon atoms, irrespective of alkoxy, amino, or alkyl substituents. Benzoic acid derivatives are readily reduced to the 1,4-dihydro derivatives. The presence of an alcohol is not necessary, in contrast to the derivatives with electron-releasing substituents. It can even result in overreduction, as the lithium alcoholate facilitates isomerization of the 1,4-dihydro product to the 3,4-dihydro isomer (eq 4).¹⁷



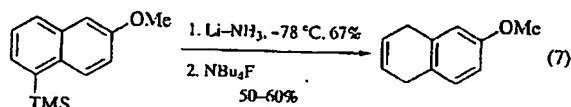
The dienolate formed during the reduction can be alkylated in situ with alkyl halides,^{18,19} epoxides,¹⁹ or α,β -unsaturated esters (eq 5)²⁰ to give 1-substituted dihydrobenzoic acids. Rearomatization provides alkyl-substituted aromatic compounds.



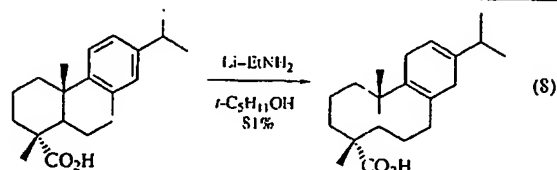
Benzamides and alkyl benzoates can be reduced to the 1,4-dihydro amides and esters, respectively, with Li-NH_3 -*t*-butanol, but K-NH_3 -*t*-butanol appears superior.¹³ However, Li may be better for in situ reductive alkylations, or K^+ may be exchanged with Li^+ before the alkylation step.²¹ Reductive methylation of *N*-benzoyl-L-prolinol derivatives afforded excellent diastereoselectivities, irrespective of the use of Li, Na, or K (eq 6).²²



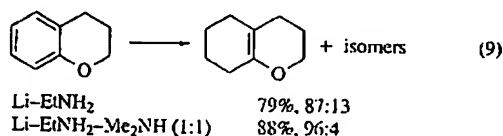
The strongly activating and easily removable trimethylsilyl group has been used to direct the regioselectivity of reduction (eq 7).²³



The Li-amine-alcohol reagents also reduce benzene derivatives to cyclohexadienes, and are usually applied when reduction in NH_3 fails.^{1h,k} Thus reduction of dehydroabiatic acid with Li-NH_3 -*t*-BuOH afforded 35% of diene while Li-EtNH_2 -*t*- $\text{C}_5\text{H}_{11}\text{OH}$ gave 81% (eq 8).²⁴ The importance of the nature of the proton source is demonstrated by the fact that neither Li-NH_3 -EtOH nor Li-EtNH_2 -EtOH gave any appreciable amount of reduction product.

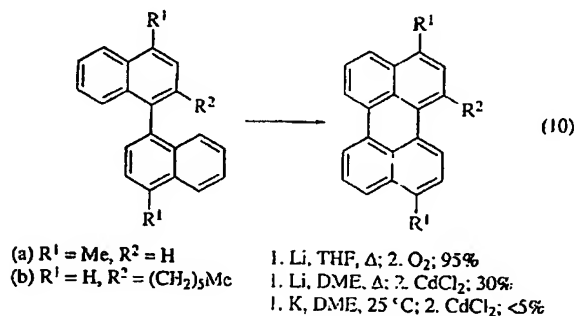


Reduction with Li-amine gives mainly cyclohexenes due to isomerization of the initially formed 1,4-diene by the strong alkylamide base.^{1h,j} Mixtures of regioisomers are formed, and best results favoring the most stable isomer are obtained with mixtures^{1h} of primary and secondary amines (eq 9).²⁵

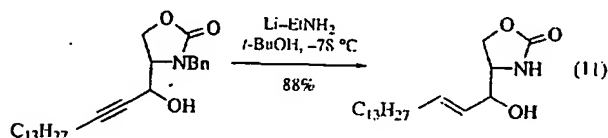


Condensed aromatic hydrocarbons are reduced more easily than those in the benzene series. Carefully chosen reaction conditions lead to the selective formation of different products.^{1b} Most extensive reductions are achieved with Li-ethylenediamine,²⁶ while Na-NH₃ is one of the mildest reagents.²⁷ Birch and Slobbe discuss the reduction of heterocyclic aromatics.^{4b}

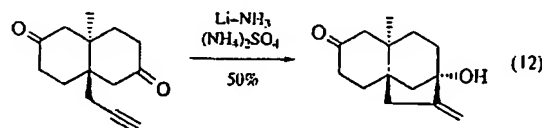
Lithium-induced cyclization of 1,1'-binaphthalenes followed by oxidation of the dianion affords perylenes.²⁸ 3,10-Dimethylperylene was obtained in 95% (eq 10a).^{28a} Cyclizations to tetrasubstituted perylenes proceeded in 36–40%,^{28b} while similar reactions with K seem somewhat higher yielding.^{29a} However, the synthesis of an 1-alkylated perylene was only successful with Li (eq 10b).^{29b}



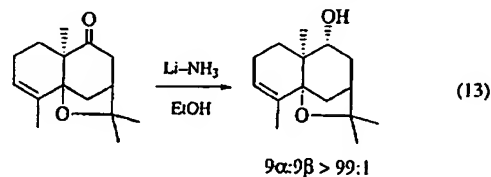
Reduction of Alkynes^{1b,h}. Internal alkynes are reduced to *trans*-alkenes with Li-NH₃ or stoichiometric amounts of Li in amines. Excess Li in amines leads to alkanes. Li-EtNH₂-*t*-BuOH efficiently reduced an alkyne precursor of sphingosine to the *trans*-alkene with simultaneous *N*-debenzylation, while triple bond reduction was incomplete with Na-NH₃ and Li-NH₃ (eq 11).³⁰



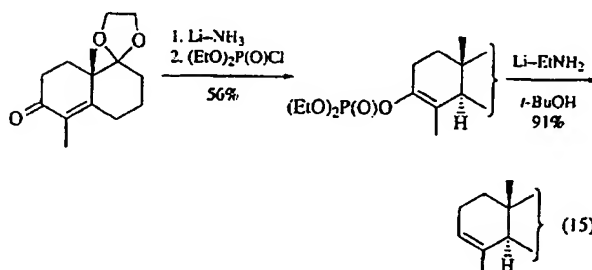
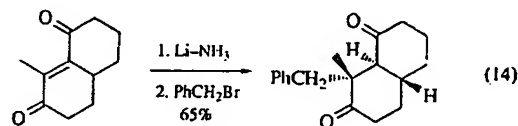
Dissolving metal reduction is the method of choice for the reduction of triple bonds in the presence of nonconjugated carboxyl groups,³¹ where *Lithium Aluminum Hydride*₄ in THF fails. Li-NH₃ afforded higher amounts of *trans*-alkenes in the reduction of some cyclic alkynes compared with Na-NH₃.³² Terminal triple bonds are protected against reduction with Li-NH₃ by deprotonation with alkali amide, but are completely reduced to double bonds by Li (or Na)-NH₃-(NH₄)₂SO₄ or by Li in amines.^{1c} Suitably located carbonyl groups give rise to cyclization, yielding vinylidenecycloalkanols,³³ e.g. eq 12.^{33a} However, the use of K^{33a,34a} or electrochemical reduction^{34b} may give better results.



Reduction of Ketones^{1a,b,1,35}. Li-NH₃-EtOH reduces sterically hindered cyclic ketones to equatorial alcohols (eq 13)³⁶ and has been widely applied in the syntheses of 11α-hydroxy steroids.³⁷ This method is complementary to complex hydride reductions, which mainly afford the axial alcohols. Bicyclo[2.2.1]heptanones are reduced predominantly to the *endo*-alcohols. Similar results have been found with Na, K, and Ca.³⁵

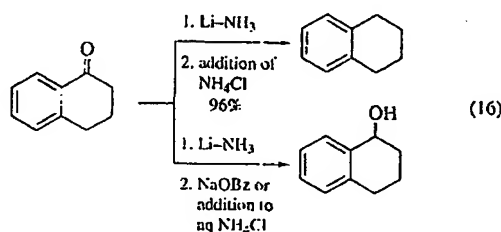


α,β-Unsaturated ketones are reduced to the ketone by Li-NH₃.^{1j} In fused ring enones the relative configuration at the ring junction is determined by protonation at the β-carbon.³⁸ Regioselective alkylation is achieved by trapping the intermediate enolate with an alkyl halide,^{39a} a strategy also applied to enediones (eq 14).^{39b} In the presence of a proton source, reduction to the saturated alcohols occurs.⁴⁰ Li-EtND₂-*t*-BuOD reduction gives high yields of saturated ketones and has been used for the stereoselective deuteration at the β-carbon.⁴¹ Conversion to alkenes is accomplished by phosphorylation of an enolate formed by Li-NH₃ reduction and subsequent hydrogenolysis with Li-EtNH₂-*t*-BuOH (eq 15).⁴²

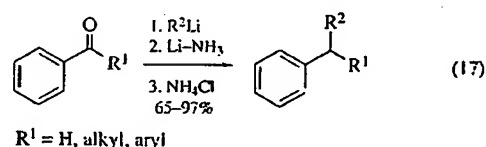


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Reductions of aromatic ketones are complicated by possible pinacol formation, reduction of the aromatic ring, and hydrogenolysis of the C–O bond. Depending on the reaction conditions, 1-tetralone is reduced to tetralin or 1-tetralol (eq 16);^{43a} in fact, seven different products can be produced.^{43b}

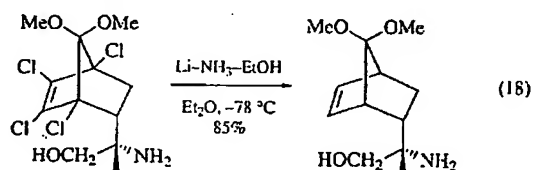


Aromatic aldehydes and ketones are alkylated and deoxygenated in a one-pot procedure using alkyl- or aryllithium, followed by Li–NH₃ (eq 17).⁴⁴



Aliphatic Carboxylic Acids. Simple straight chain carboxylic acids are reduced by Li–MeNH₂ or Li–NH₃ to an intermediate imine which can either be hydrolyzed to the aldehyde or catalytically reduced to the amine.⁴⁵

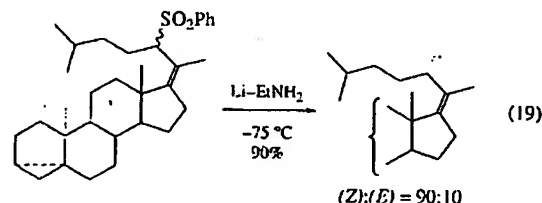
Reductive Cleavage of Polar Single Bonds^{1a}. Li in various solvents provides effective reagents for the cleavage of polar single bonds. The cleavage tendency decreases in the order C–I > C–Br > C–Cl > C–S > C–O > C–N > C–C. Polyhalo compounds are completely reduced with Li and *t*-BuOH in THF (Winstein procedure).⁴⁶ Allylic, geminal, bridgehead, and vinylic halogen atoms are removed, the latter stereospecifically. NH₃ and amines have been avoided as solvents due to potential reaction with the alkyl halides by elimination or substitution.^{1a, 47a} However, Li–NH₃ systems successfully reduce vinylic, bridgehead, and cyclopropyl halides^{47b, c} and sometimes give better results than the Winstein–Gassman procedures (eq 18).^{47c}



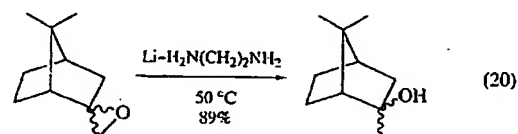
Alkylolithium reagents nowadays often replace Li for the preparation of organolithium compounds from alkyl or aryl bromides.⁴⁸ Li has been used to couple alkyl and aryl halides in Wurtz or Wurtz–Fittig-type reactions,⁴⁹ though the use of Na is much more important. Reduction of monosubstituted alkyl halides or selective reduction of geminal dihalides are best carried out with metal or complex hydrides or by catalytic hydrogenation.^{1b}

Sulfides, sulfoxides, and sulfones are reductively cleaved with lithium.⁵⁰ Reduction of sulfides in THF is improved with catalytic naphthalene. Li–EtNH₂ gave better results than Sodium Amalgam

for the cleavage of the C–S bond in sulfones (eq 19),^{51a, b} and than Raney Nickel for some sulfide cleavage.^{51c} Selenides are cleaved similarly.⁵² Thio- and selenoacetals are reduced to alkanes.



Allyl, benzyl, and aryl ethers are cleaved by Li in NH₃ or amines.^{1a, b} Sterically hindered steroid epoxides, which are not cleaved with LiAlH₄, are converted into axial alcohols by Li–EtNH₂.^{1b} Li–ethylenediamine efficiently cleaves sterically hindered epoxides to tertiary alcohols (eq 20).⁵³



Li promoted reductions of allyloxy and benzyloxy esters^{54a} and esters of sterically hindered secondary and tertiary alcohols^{54b} give rise to carboxylate cleavage, thus presenting a means of indirect deoxygenation of alcohols. Further reductive cleavages have been found with activated cyclopropanes,⁵⁵ *N*-oxides,⁵⁶ and sulfonamides.⁵⁷

Li (and K) promoted reduction of TiCl₃ in the McMurry reaction has been reported to be more reliable than the TiCl₃/LiAlH₄ reagent.⁵⁸

Related Reagents. See Classes R-2, R-4, R-7, R-12, R-14, R-15, R-23, R-25, R-27, R-28, R-29, R-30, and R-32, pages 1–10. Calcium; Lithium–Ethyamine; Potassium; Sodium; Sodium–Alcohol; Sodium–Ammonia.

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FIFTH EDITION

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Professor of Chemistry, Adelphi University



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liberates the free ethynyl naphthalenide and $\text{NiCl}_2 \cdot \text{I}_2\text{CH}_3$.³⁵³ This reagent is a mixture of NaBH_4 and BiCl_3 reduced to an alkene, in the presence of $\text{Cp}_2\text{Zr(H)Cl}$.³⁵⁶ DIBAL-H ,³⁵⁸ and by

amines, the mechanism of reduction with trifluoroborane coming in from the acid is, the reaction can be a tertiary carbocation or an alkene.³⁶¹ It has been shown, styrene by hydridopentadiene.³⁶²

with DIBAL-H usually triple-bond reduction lead to the cis products. However, this is not the case with the reductions with LiAlH_4 and NaBH_4 , as well as NaH , reduce ordinary alkenes and alkynes when complexed with transition metal salts, such as FeCl_2 or CoBr_2 .³⁸⁹ The $\text{C}=\text{C}$ unit proximal to the carbonyl in dienyl amides is selectively reduced with NaBH_4/I_2 .³⁹⁰ Silanes can be effective for the reduction of the $\text{C}=\text{C}$ unit in conjugated systems in the presence of copper species.³⁹¹

hydrogenation.³⁶⁵ In this molecule, which is itself homogeneous, is frequently which, when a palladium hydrogen.

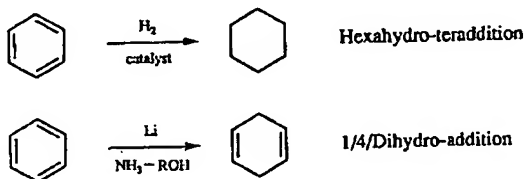
II, 586, 742; IV, 136, 302,

reduce double bonds in $\text{C}=\text{O}$ bonds, for example,³⁶⁷

NaBH_4 has a greater tendency than LiAlH_4 to effect this double reduction, though even with NaBH_4 the product of single reduction (of the $\text{C}=\text{O}$ bond) is usually formed in larger amount than the doubly reduced product. The LiAlH_4 gives significant double reduction only in cinnamyl systems, (e.g., with $\text{PhCH}=\text{CHCOOH}$).³⁶⁸ Asymmetric catalytic hydrogenation has been reported for conjugated carboxylic acids³⁶⁹ and conjugated ketones.³⁷⁰

Reduction of only the $\text{C}=\text{C}$ bond of conjugated $\text{C}=\text{C}-\text{C}=\text{O}$ and $\text{C}=\text{C}-\text{C}\equiv\text{N}$ systems³⁷¹ has been achieved by many reducing agents,³⁷² a few of which are H_2 and a Rh catalyst,³⁷³ PhSiH_3 and a nickel catalyst³⁷⁴ or CuCl ,³⁷⁵ $\text{PhSiH}_3-\text{Mo(CO)}_6$,³⁷⁶ $\text{NaBH}_4-\text{BiCl}_3$,³⁷⁷ borohydride exchange resin, $(\text{BER})-\text{CuSO}_4$,³⁷⁸ SmI_2 ,³⁷⁹ and catecholborane.³⁸⁰ See 16-23 for methods of reducing $\text{C}=\text{O}$ bonds in the presence of conjugated $\text{C}=\text{C}$ bonds. The $\text{C}=\text{C}$ unit of conjugated aldehydes has been reduced using AlMe_3 with a catalytic amount of CuBr ³⁸¹ and with ammonium formate/ $\text{Pd}-\text{C}$.³⁸² Selective reduction of the $\text{C}=\text{C}$ unit in conjugated ketones was accomplished with $\text{Na}_2\text{S}_2\text{O}_4$ in aqueous dioxane, and nonconjugated alkenes were not reduced.³⁸³ Lithium aluminium hydride also reduces the double bonds of allylic alcohols³⁸⁴ and NaBH_4 in $\text{MeOH}-\text{THF}$ ³⁸⁵ or NaCNBH_3 on a zeolite³⁸⁶ reduces α,β -unsaturated nitro compounds to nitroalkanes. Baker's yeast reduces conjugated nitro compounds to nitroalkanes³⁸⁷ and the $\text{C}=\text{C}$ unit of conjugated ketones.³⁸⁸ Furthermore, both LiAlH_4 and NaBH_4 , as well as NaH , reduce ordinary alkenes and alkynes when complexed with transition metal salts, such as FeCl_2 or CoBr_2 .³⁸⁹ The $\text{C}=\text{C}$ unit proximal to the carbonyl in dienyl amides is selectively reduced with NaBH_4/I_2 .³⁹⁰ Silanes can be effective for the reduction of the $\text{C}=\text{C}$ unit in conjugated systems in the presence of copper species.³⁹¹

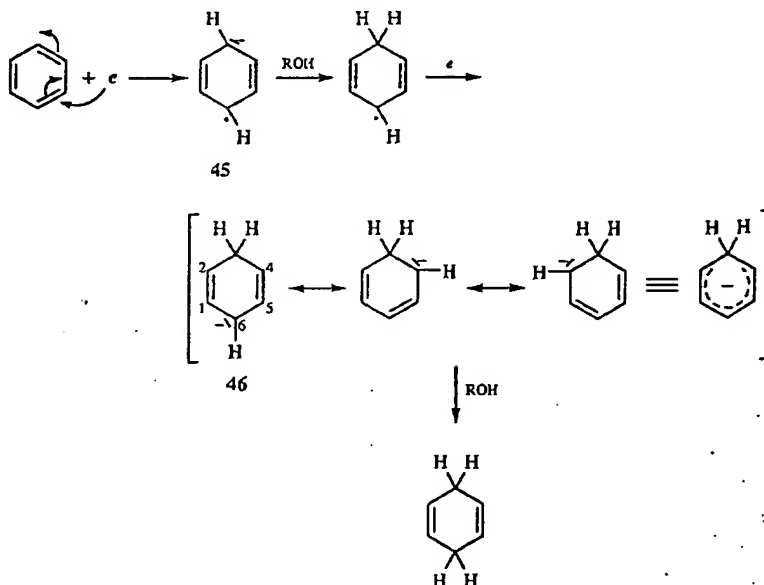
15-14 Hydrogenation of Aromatic Rings



Aromatic rings can be reduced by catalytic hydrogenation,³⁹² but higher temperatures (100–200°C) are required than for ordinary double bonds.³⁹³ Though the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.³⁹⁴ Mild conditions are also successful in hydrogenations with phase-transfer catalysts.³⁹⁵ Many functional groups, such as OH , O^- , COOH , COOR , and NH_2 , do not interfere with the reaction, but some groups may be preferentially reduced. Among these are CH_2OH groups, which undergo hydrogenolysis to CH_3 (10-81). Phenols may be reduced to cyclohexanones, presumably through the enol. Heterocyclic compounds are often reduced. Thus furan gives tetrahydrofuran. With benzene rings it is usually impossible to stop the reaction after only one or two bonds have been reduced,

since alkenes are more easily reduced than aromatic rings.³⁹⁶ Thus, 1 mol of benzene, treated with 1 mol of hydrogen, gives no cyclohexadiene or cyclohexene but $\frac{1}{3}$ mol of cyclohexane and $\frac{2}{3}$ mol of recovered benzene. This is not true for all aromatic systems. With anthracene, for example, it is easy to stop after only the 9,10-bond has been reduced (see p. 49). Hydrogenation of phenol derivatives can lead to conjugated cyclohexenones.³⁹⁷

When aromatic rings are reduced by lithium (or potassium or sodium) in liquid ammonia (such reductions are known as *dissolving metal reductions*), usually in the presence of an alcohol (often ethyl, isopropyl, or *tert*-butyl alcohol), 1,4 addition of hydrogen takes place and nonconjugated cyclohexadienes are produced.³⁹⁸ This reaction is called the *Birch reduction*.³⁹⁹ Heterocycles such as pyrroles⁴⁰⁰ and furans⁴⁰¹ can be reduced using Birch reduction. Ammonia obtained commercially often has iron salts as impurities that lower the yield in the Birch reduction. Therefore, it is often necessary to distill the ammonia. When substituted aromatic compounds are subjected to the Birch reduction, electron-donating groups such as alkyl or alkoxy decrease the rate of the reaction and are generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene, not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups such as COOH or CONH₂ increase the reaction rate and are found on the reduced positions of the product.⁴⁰² The regioselectivity of the reaction has been examined.⁴⁰³ The mechanism involves solvated electrons,⁴⁰⁴ which are transferred from the metal to the solvent, and hence to the ring.⁴⁰⁵



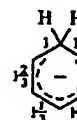
The sodium becomes oxidized to Na⁺ and creates a radical ion (45).⁴⁰⁶ There is a great deal of evidence from ESR spectra for these species.⁴⁰⁷ The radical ion accepts

a proton from the alcohol to give a another sodium atom. Finally, 46 ac alcohol is to supply protons, since enough for this purpose. In the at dimerization of 45 are frequently ob substrates, (e.g., biphenyl) that the rac carbanion corresponding to 46 by a di is reversed: first a second electron is g a proton, producing the intermediate

Indium metal reduces the pyri solution.⁴⁰⁹ Samarium iodide (SmI phenol in MeOH/KOH.⁴¹¹

Ordinary alkenes are usually ur double bonds may be present in the m However, phenylated alkenes, intern (with C=C or C=O) are reduced un

Note that 46 is a resonance hyt canonical forms shown. The question up a proton at the 6 position to give t the 1,3-diene?⁴¹² An answer to this q suggested that this case is an illustr motion.⁴¹³ According to this principl that involve the least change in ato The principle can be applied to the ca: The VB bond orders (p. 32) for the si each of the three forms contributes ex $\frac{1}{3}$, and $\frac{1}{3}$. When the carbanion is com follows:



It can be seen that the two bonds w products, but for the other four bond: the change is $\frac{1}{3} + \frac{1}{3} + \frac{1}{3} + \frac{1}{3}$, while for $\frac{1}{3} + \frac{2}{3} + \frac{2}{3} + \frac{1}{3}$. Since a greater change of least motion predicts formation of because the ¹³C NMR spectrum of a greater electron density than the 2 former more attractive to a proton.⁴¹⁴

ONDS

CHAPTER 15

REACTIONS 1011

aromatic rings.³⁹⁶ Thus, 1 mol of no cyclohexadiene or cyclohexene 1 benzene. This is not true for all it is easy to stop after only the 9,10- of phenol derivatives can lead to

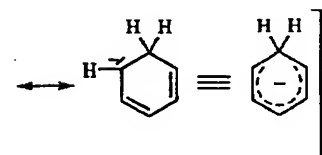
(or potassium or sodium) in liquid *ig metal reductions*), usually in the *tert*-butyl alcohol), 1,4 addition of hexadienes are produced.³⁹⁸ This *rocycles* such as pyrroles⁴⁰⁰ and Ammonia obtained commercially the yield in the Birch reduction. monia. When substituted aromatic, electron-donating groups such as on and are generally found on the *iple*, anisole gives 1-methoxy-1,4-iene. On the other hand, electron-increase the reaction rate and are The regioselectivity of the reaction *s solvated electrons*,⁴⁰⁴ which are *nence to the ring*.⁴⁰⁵

a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, 46 accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of 45 are frequently obtained. There is evidence⁴⁰⁸ at least with some substrates, (e.g., biphenyl) that the radical ion corresponding to 45 is converted to the carbanion corresponding to 46 by a different pathway, in which the order of the steps is reversed: first a second electron is gained to give a dianion,⁴⁰⁶ which then acquires a proton, producing the intermediate corresponding to 46.

Indium metal reduces the pyridine ring in quinoline in aqueous sethanol solution.⁴⁰⁹ Samarium iodide (SmI_2) reduces pyridine in aqueous THF⁴¹⁰ and phenol in MeOH/KOH.⁴¹¹

Ordinary alkenes are usually unaffected by Birch-reduction conditions, and double bonds may be present in the molecule if they are not conjugated with the ring. However, phenylated alkenes, internal alkynes (p. 1009), and conjugated alkenes (with $\text{C}=\text{C}$ or $\text{C}=\text{O}$) are reduced under these conditions.

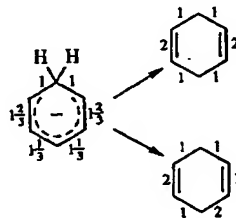
Note that 46 is a resonance hybrid; that is we can write the two additional canonical forms shown. The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position to give the 1,3-diene?⁴¹² An answer to this question has been proposed by Hine,⁴¹³ who has suggested that this case is an illustration of the operation of the *principle of least motion*.⁴¹³ According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."⁴¹³ The principle can be applied to the case at hand in the following manner (simplified): The VB bond orders (p. 32) for the six carbon-carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, and $1\frac{1}{3}$. When the carbanion is converted to the diene, these bond orders change as follows:



ROH



ates a radical ion (45).⁴⁰⁶ There is a e species.⁴⁰⁷ The radical ion accepts



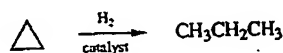
It can be seen that the two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is $\frac{1}{3} + \frac{1}{3} + \frac{1}{3} + \frac{1}{3}$, while formation of the 1,3-diene requires a change of $\frac{1}{3} + \frac{2}{3} + \frac{2}{3} + \frac{1}{3}$. Since a greater change is required to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene. This may not be the only factor, because the ^{13}C NMR spectrum of 46 shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.⁴¹⁴

1012 ADDITION TO CARBON-CARBON MULTIPLE BONDS

Reduction of aromatic rings with lithium⁴¹⁵ or calcium⁴¹⁶ in amines (instead of ammonia—called *Benkeser reduction*) proceeds further and cyclohexenes are obtained. It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced.⁴¹⁷ Lithium triethylborohydride (LiBET_3H) has also been used, to reduce pyridine derivatives to piperidine derivatives.⁴¹⁸

OS I, 99, 499; II, 566; III, 278, 742; IV, 313, 887, 903; V, 398, 400, 467, 591, 670, 743, 989; VI, 371, 395, 461, 731, 852, 856, 996; VII, 249.

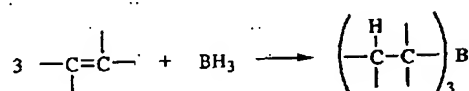
15-15 Reductive Cleavage of Cyclopropanes



Cyclopropanes can be cleaved by catalytic hydrogenolysis.⁴¹⁹ Among the catalysts used have been Ni, Pd, and Pt. The reaction can often be run under mild conditions.⁴²⁰ Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,⁴²¹ can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.⁴²² Similar reduction has been accomplished photochemically in the presence of LiClO_4 .⁴²³

F. A Metal on the Other Side

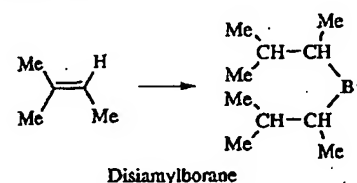
15-16 Hydroboration



When alkenes are treated with borane⁴²⁴ in ether solvents, BH_3 adds across the double bond.⁴²⁵ Borane cannot be prepared as a stable pure compound⁴²⁶ (it dimerizes to diborane B_2H_6), but it is commercially available in the form of complexes with THF, Me_2S ,⁴²⁷ phosphines, or tertiary amines. The alkenes can be treated with a solution of one of these complexes (THF-BH_3 reacts at 0°C and is the most convenient to use; $\text{R}_3\text{N-BH}_3$ generally require temperatures of $\sim 100^\circ\text{C}$; however, the latter can be prepared as air stable liquids or solids, while the former can only be used as relatively dilute solutions in THF and are decomposed by moisture in air) or with a mixture of NaBH_4 and BF_3 etherate, which generates borane *in situ*.⁴²⁸ Ordinarily, the process cannot be stopped with the addition of one molecule of BH_3 because the resulting RBH_2 adds to another molecule of alkene to give R_2BH , which in turn adds to a third alkene molecule, so that the isolated product is a trialkylborane (R_3B). The reaction can be performed on alkenes with one to four substituents, including cyclic alkenes, but when the alkene is moderately hindered, the product is the dialkylborane R_2BH or even the monoalkylborane RBH_2 .⁴²⁹ For example, 47 (*disiamylborane*) and 48 (*thexylborane*)⁴³⁰ have been

CHAPTER 15

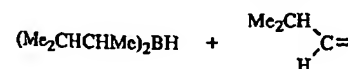
prepared in this manner. Monoalkylb hindered alkenes, as above) and dialkyl



47

the mixed trialkylboranes $\text{RR}'_2\text{B}$ or methylborane (MeBH_2),⁴³¹ which is solvent THF, the reaction can be stopped with boranes (RMeBH).⁴³² Reaction of thi borane ($\text{RR}'\text{MeB}$).⁴³³ Other monoalkyl BuBH_2 , behave similarly with internal $\text{RCH}=\text{CH}_2$.⁴³⁴

In all cases, the boron goes to the less hindered side, whether the substituents are aryl or alkyl. Markovnikov's rule, since boron is more positive than carbon, is caused mostly by steric factors, though the effect of ring substituents on the regioselectivity of substituted styrenes showed characteristic behavior.⁴³⁶ When both sides of the double bond are disubstituted, about equal amounts of the two possible products are made in such cases to make the reaction attacking molecule. For example, treatment of 2-pentene with 47 gave 95% 45



47

Another reagent with high regioselectivity which is prepared by hydroboration of



The 9-BBN has the advantage that it attacks all sorts of double bonds. Disiamyl

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